

REMARKS

I. Amendments and Status of the Claims

Claims 1, 2, and 7-27 were pending, with claims 1 and 27 being independent.

Claims 1 and 27 have been amended, without prejudice to pursue any canceled subject matter in a continuing application, and without disclaimer of any subject matter. Support for the amendments to claims 1 and 27 can be found throughout the specification and original claims. In particular, claims 1 and 27 have been amended to recite that the cells are "MDCK cells that are attached to a substrate." The specification on page 5, line 13, for example, indicates that the cells used in the method can be MDCK cells. Original claim 5 and the specification on page 3, lines 6-10, describe the use of a substrate for the culture of anchorage-dependent cells. Support for the amendment of claims 1 and 27 to recite "at least one virus" can be found, among other places, in the specification on page 2, lines 34-36, the Examples, and in original claim 6, which locations all provide support for this amendment. Claim 1 has also been amended to recite the proportion of cells used in the first and second parts. The specification, at least on page 4, lines 9-13, describes using the recited ratio of cells, as does Figure 1 and many of the Examples.

In view of the amendments to claim 1, claims 9, 10, 19-22, and 26 have been canceled without prejudice to pursue the subject matter of these claims in a continuing application, and without disclaimer of any subject matter. Claim 11 has been amended to remove duplicative subject matter and to correct reference to a previous step.

These amendments add no new matter. Claims 1, 2, 7, 8, 11-18, 23-25, and 27 are pending and under consideration.

II. Claim Rejection under 35 U.S.C. § 103

Claims 1, 2, and 7-27 stand rejected as allegedly unpatentable over BRYAN GRIFFITHS & DENIS LOOBY, *Scale-Up of Suspension and Anchorage-Dependent Animal Cells*, in 75 METHODS IN MOLECULAR BIOLOGY: BASIC CELL CULTURE PROTOCOLS 59 (Jeffrey W. Pollard & John M. Walker eds., 2d ed. 1997) ("*Griffiths*") and JEFFREY W. POLLARD, *Basic Cell Culture*, in 75 METHODS IN MOLECULAR BIOLOGY: BASIC CELL CULTURE PROTOCOLS 1 (Jeffrey W. Pollard & John M. Walker eds., 2d ed. 1997) ("*Pollard*"). April 20, 2005, Final Office Action, page 2.

Applicant respectfully traverses this rejection. A *prima facie* case of obviousness must satisfy several criteria, including that the prior art references must teach or suggest all of the claim limitations and that there is some reason, suggestion, or motivation in the prior art to lead one of ordinary skill in the art to combine the teachings of the references in the manner proposed by the Office. M.P.E.P. § 2143. The suggestion to combine the prior art teachings must be clear and particular. *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999). Further, the suggestion to combine reference teachings cannot "be resolved on subjective belief and unknown authority." *In re Lee*, 61 U.S.P.Q.2d 1430, 1434 (Fed. Cir. 2002).

In *Lee*, claims directed to a method for automatically displaying functions of a video display device were rejected as obvious over a combination of references. *Id.* at 1431. In affirming the rejection, the Board asserted that "[t]he conclusion of obviousness may be made from common knowledge and common sense of a person of ordinary skill in that art without any specific hint or suggestion in a particular reference." *Id.* at 1432. The Federal Circuit disagreed, however, finding that "[t]he examiner's

conclusory statements . . . do not adequately address the issue of motivation to combine. This factual question of motivation is material to patentability, and could not be resolved on subjective belief and unknown authority.” *Id.* at 1434.

Here, Applicant submits that the alleged motivation to combine the teachings of *Griffiths* and *Pollard* is also a conclusion grounded in the allegedly common sense notion that “[i]t would have been obvious at the time the invention was made to use a production batch with any passage number wherein the cells maintain the desired phenotype and/or production capabilities.” April 20, 2005, Final Office Action, pages 2-3. Moreover, *Griffiths* and *Pollard*, both when taken alone and in combination, fail to teach all of the claim limitations of the present claims. Accordingly, the Office has not met its burden for establishing a *prima facie* case of obviousness.

A. Passage Number Is Relevant to Obviousness Question

The Office alleges that “[i]t would have been obvious at the time the invention was made to use a production batch with any passage number wherein the cells maintain the desired phenotype and/or production capabilities.” April 20, 2005, Final Office Action, pages 2-3. Although the Office does not explain the basis for its assertion, it appears that the Office is relying on the alleged common sense assertion that one could use any passage number of cells, so long as that passage number had the desired phenotype. This “common sense” approach does not, however, adequately address why the ordinary artisan would have been motivated to use cells from different passages for the production of at least one virus. See *Lee*, 61 U.S.P.Q.2d at 1434.

Applicant respectfully contends that passage number is a relevant consideration to the patentability of the pending claims. As previously noted, without Applicant's invention, the production of viruses for vaccines has required the growth of a vast array of cells, all having the same passage number. See, e.g., U.S. Pat. No. 4,664,912 to Wiktor *et al.* ("*Wiktor*"), at col. 2, lines 68-69; see also Specification, page 1, lines 15-20, and page 4, lines 26-34. As Applicant explains: "In classical serial production lines the number of doubling of the cells derived from the MWCS at the moment of harvest is known up front within certain limits. A maximum allowable generation number is set to the production system at the onset." Specification, page 4, lines 15-17.

Wiktor provides an example of the type of production protocol used prior to Applicant's invention. *Wiktor* teaches that it is conventional to employ only the same passage numbers across all production batches.

Preferably, in starting with the VERO working seed, a passage is effected in a 1 liter bioreactor. The cells are obtained by digestion with a very purified and diluted protease solution, then a passage is effected in a 5 liter bioreactor; then a new passage is effected in a 25 liter bioreactor; then a new passage is effected in a 150 liter bioreactor, and a last passage is effected with the use of a bioreactor of very large volume (for example 1000 liters), or a plurality of bioreactors of smaller volume (for example 150 liters), the inoculation by the virus being effected in this last passage.

Wiktor, col. 2, lines 58-69. In that method, vessel upon vessel of cells all having the same passage number were prepared, and then seeded with virus for the production of vaccine. The production number had to be the same for every production batch. Thus, the need to use the same production passage number created an enormous logistical

problem of managing preproduction batches and harvesting the virus at the optimum time.

In contrast to prior art methods, Applicant's inventive method do not require strict adherence to production passage number. Indeed, "[p]roduction passage number (the number of cell passages used prior to production of the biological product), hence, is irrelevant within the limits set by ECB." Specification, page 4, lines 20-21. This statement does not suggest, however, that passage number is completely "irrelevant," as alleged by the Office. Instead, production passage number according to the present invention is "irrelevant" in the sense that the same passage number is no longer required in all production batches. As Applicant explains, "[o]nce such ECB is fully characterised one may allow to produce the product with cells at any passage number between MCB and ECB[.]" Specification, page 4, lines 29-31. Therefore, a different passage number can be used in a production batch and the logistical problems encountered in prior art methods can be mitigated.

The cited documents, *Griffiths* and *Pollard*, do not teach or suggest that cells having different passage numbers can be used in a production batch. The Office alleges that "[i]t would have been obvious at the time the invention was made to use a production batch with any passage number wherein the cells maintain the desired phenotype and/or production capabilities." April 20, 2005, Final Office Action, pages 2-3. The Office, however, offers no support for this assertion. Thus, as was the case in *Lee*, the Office has not pointed to any authority to support its position. Evidence, and not just speculation, is required to support a grounds of rejection. See M.P.E.P. § 2144.03 (requiring substantial evidence to support grounds of rejection).

Further, Applicant again notes that, even if, as alleged by the Office, “any” passage number might be used, this still does not suggest that different passage numbers can or should be used. That is, there is no suggestion or motivation for combining different passage numbers, as recited in the claimed methods, for the production of viruses.

B. Griffiths and Pollard Do Not Teach All Claim Elements

As discussed, the Office does not point to any teaching or suggestion in *Griffiths* or *Pollard* that cells of different production passage number can be used in the production of viruses. In addition, however, the amended claims recite additional elements neither taught nor suggested by the asserted combination of references.

Although *Griffiths* mentions scale up of cells for production of viruses, this is only as a passing reference in the “Introduction” and no details are given. In particular, there is no teaching or suggestion that the cells should be MDCK cells that are cultured on a substrate. Further, and consistent with the references’ failure to teach a method that results in production cells of different passage numbers, neither *Griffiths* nor *Pollard*, whether taken alone or in combination, teach or suggest the split ratio now recited in claim 1.

The cited references, therefore, when considered alone or in combination, do not teach all of the claim elements. In addition, the Office has not provided any evidentiary support for its assertion that it would have been obvious to use cells of any passage number. Applicants reiterate that the use of “any” passage number is not the same as the use of a different passage number. In addition, Applicant has pointed to evidence

that prior art methods routinely used cells of the same passage number for the production of viruses, whereas the recited methods use cells of different passage numbers. Accordingly, Applicant respectfully submits that a *prima facie* case of obviousness has not been made. This rejection should therefore be withdrawn.

C. Unexpectedly Facile Production of Viruses

As explained above, Applicant respectfully contends that a *prima facie* case of obviousness has not been made. Nonetheless, to further show that the claimed methods are patentable, Applicant again points to the unexpected results of his useful, new, and non-obvious invention. In particular, “[t]he method described allows high through-put production since the up scaling route from WCS to production cells can be very much shortened and much less bioreactors are needed since parallel production lines are not needed anymore.” Specification, page 3, line 35 to page 4, line 2. In contrast to prior art methods, such as that described in *Wiktor*, this can represent a significant savings in time, resource allocation, and money, resulting in smaller and better-controlled growth and harvesting processes, particularly for viruses. Applicant submits that the claimed method thus results in an unexpectedly facile method for the production of viruses. Accordingly, this evidence is relevant to the issue of obviousness and must be considered. M.P.E.P. 2141.III.

For all of these reasons, Applicant respectfully requests that the rejection be withdrawn and the pending claims be allowed.

CONCLUSION

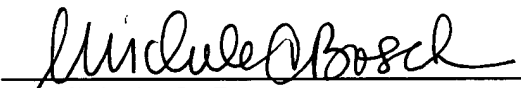
In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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